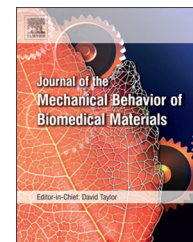


Available online at [www.sciencedirect.com](http://www.sciencedirect.com)**ScienceDirect**[www.elsevier.com/locate/jmbbm](http://www.elsevier.com/locate/jmbbm)**Research Paper****Intrinsic viscoelasticity increases temperature in knee cartilage under physiological loading**

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**ABSTRACT**

Metabolism of proteoglycans and hyaluronic acid has been shown to be temperature-dependent in cartilage explants, with optimal anabolic effects between 36 °C and 38 °C. At rest, the temperature of human knee has a value of around 33 °C. We aim to show in this study that viscoelastic properties of healthy human cartilage allow its temperature to reach those optimal temperatures during physiological mechanical loadings. We developed a model allowing to determine the temperature increase in cartilage due to viscous dissipation. The model had three parameters, which were determined experimentally. The first parameter was the energy dissipated by cartilage samples submitted to cyclic stimulation. It was obtained with standard in vitro mechanical testing. The second parameter was the cartilage heat capacity and was measured in vitro with differential scanning calorimetry. Finally, the third parameter was the time constant of cartilage heat transfer and was obtained with in vivo magnetic resonance thermometry performed on four volunteers. With these experimentally determined parameters, the model predicted that cartilage dissipation is sufficient to raise the temperature in healthy knee cartilage from 33 °C to 36.7 °C after a 1 h walking. These results showed that intrinsic viscoelastic properties of the cartilage could induce a temperature increase optimal for the production of proteoglycans and hyaluronic acid. Interestingly, degenerated cartilage did not present high enough viscoelastic properties to significantly induce a temperature increase. Taken together, these data suggest an association between cartilage dissipation and its homeostasis.

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**1. Introduction**

Temperature is a fundamental quantity in mechanics. However, most of the works performed in biomechanics considers the studied processes as isothermal due to the fact that mammals have a regulated system for maintaining their

temperature constant (Romanovsky, 2007). The isothermal hypothesis may be locally wrong when considering viscoelastic tissues submitted to dynamic loading. Indeed, viscoelastic materials dissipate part of the mechanical energy into heat, creating thus an internal heat source in the materials (Ratner and Korobov, 1966). The corresponding effect may be

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spectacular, as it has been shown that an increase in temperature of 6.5 °C can be generated between the outer and inner parts of a horse tendon during intense running (Wilson and Goodship, 1994). The avascular region of the tendon was the site of the most marked temperature increase. This observation suggests that the key point to obtain an increase in temperature in a tissue is an insufficient blood supply to transport the generated heat.

Given that articular knee cartilage is avascular (Oldershaw, 2012) and has viscoelastic properties (Hayes and Mockros, 1971; Huang et al., 2003), a local temperature increase in the cartilage could then be obtained due to dissipation following a cyclic mechanical loading. This is especially interesting since it has been shown that increasing temperature affects the metabolism of cells. Indeed, the rate of proteoglycan synthesis and the release of newly synthesized proteoglycans by chondrocytes are increased in cultures at 37 °C compared to 32 °C (Brand et al., 1991). Likewise, for the same temperature increase the rates of hyaluronic acid synthesis and glycolysis are also enhanced (Castor and Yaron, 1976).

The knee temperature at rest has a value of around 33 °C in healthy human subjects (Becher et al., 2008; Harris and McCroskery, 1974). A temperature close to 37 °C due to dissipation subsequent to a mechanical loading would enhance the metabolism of chondrocytes.

In this study, we aim to verify if cartilage dissipation under mechanical loading is sufficient to raise temperature from 33 °C to temperatures close to 37 °C, at which proteoglycan and hyaluronic acid metabolisms are optimal. As well, we aim to evaluate if a degeneration of cartilage will also affect temperature increase, since mechanical dissipation is dependent to the matrix microstructure and composition.

## 2. Material and methods

### 2.1. Experimental design

In order to determine the temperature increase in cartilage under mechanical loading due to its intrinsic viscoelastic properties, a mathematical model was developed. The model encompassed three parameters determined experimentally (Fig. 1). The first parameter was the power of energy dissipated subsequent to a mechanical loading, which was quantified in vitro on human cartilage samples. The second parameter was the cartilage heat capacity, which was measured in vitro on human cartilage samples with differential scanning calorimetry. Finally, the third parameter was the time constant of cartilage heat transfer. This time constant was determined on four volunteers by magnetic resonance thermometry.

As viscoelastic properties are related to material microstructure (Shaw and MacKnight, 2005), we quantified the energy dissipation of human cartilage samples taken from different sites of the femoral head of subjects who underwent hip arthroplasty. We defined each sample as “healthy” or “degenerated” depending on their dynamic stiffness. Indeed, it has been shown that in osteoarthritic cartilage dynamic stiffness is 70% lower than in healthy cartilage (Knecht et al., 2006).

The influence of cartilage degeneration on temperature increase was then assessed.

### 2.2. Mathematical model

The model that determined temperature evolution in a material under mechanical loading is derived from the heat equation (Dinzart et al., 2008)

$$mc \frac{\partial T(x, t)}{\partial t} = k \nabla^2 T(x, t) + \dot{Q} \quad (1)$$

where in our particular case,  $m$  is the cartilage mass,  $c$  its heat capacity,  $k$  its conductivity and  $\dot{Q}$  its energy dissipation when subject to cyclic loading.

As our cartilage samples are thin, the temperature distribution in the system can be assumed as quasi-uniform (Dinzart et al., 2008). Therefore Eq. (1) is reduced to

$$mc \frac{dT(t)}{dt} + \lambda S(T(t) - T_0) = \dot{Q} \quad (2)$$

where  $k \nabla^2 T(x, t)$  is simplified to  $\lambda S(T(t) - T_0)$  when averaged over the cartilage thickness. The heat flux represents the heat transfer out of the cartilage surface  $S$ .  $\lambda$  is the heat transfer coefficient at the system frontier and  $T_0$  the temperature outside the system, which value is 33 °C, corresponding to knee joint temperature at rest (Harris and McCroskery, 1974).

Cartilage dissipation is determined by hysteresis stress-strain curve (Szarko et al., 2010)

$$\dot{Q} = Hf \quad (3)$$

where  $H$  is the area enclosed by cartilage hysteresis curve and  $f$  the loading frequency.

Combining Eqs. (2) and (3) the temperature evolution becomes

$$mc \frac{dT(t)}{dt} = Hf - \lambda S(T(t) - T_0) \quad (4)$$

Eq. (4) can be rewritten as

$$\begin{cases} \dot{T} + aT = b \\ T(t_0) = T_i \end{cases} \quad (5)$$

Identifying the constants  $a$  and  $b$  with the parameters of Eq. (4), the analytical solution of Eq. (5) is then given by

$$\begin{cases} T(t) = \frac{be^{at} + (aT_i - b)e^{at_0}}{ae^{at}} \\ a = \frac{\lambda S}{mc} \\ b = \frac{Hf + \lambda ST_0}{mc} = \frac{Hf}{mc} + aT_0 \end{cases} \quad (6)$$

The only unknowns appearing in Eq. (6) are the constant  $a$  that is the inverse of time constant of heat transfer, the dissipation power  $Hf$  and the heat capacity  $c$ , all of which are experimentally determined.

### 2.3. Dissipation power of cartilage obtained with uniaxial compression test

Human cartilage samples ( $n=6$ ) were punched (8 mm diameter) from the femoral head of donors who have undergone hip arthroplasty (Centre Hospitalier Universitaire Vaudois Ethics Committee Protocol # 264/12). The samples were taken from different sites, three samples were punched close to the site of degeneration (<2 cm), and the others more than 2 cm

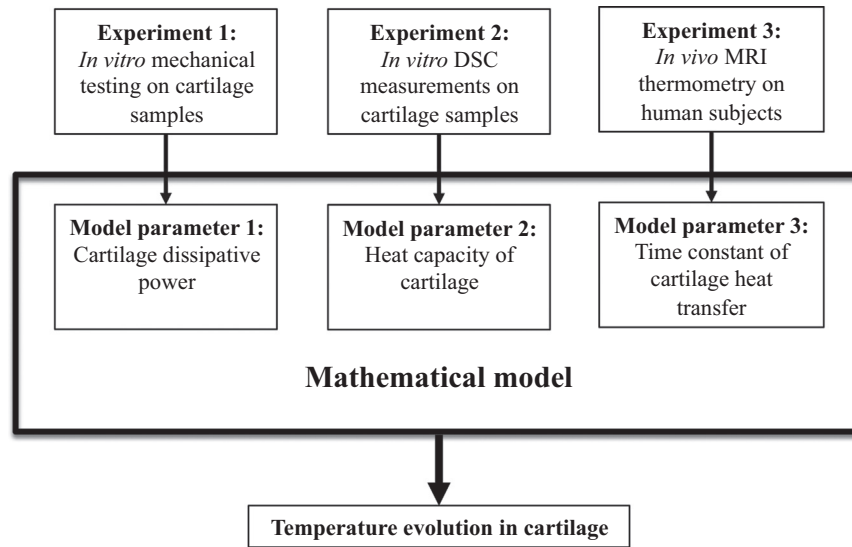


Fig. 1 – Flowchart of the experiments used to determine the three parameters appearing in the model of temperature evolution in the cartilage.

Table 1 – Summary of the MR sequence.

TR/TE (ms)	FA (°)	Acquisition matrix	Slice thick. (mm)	Pixel size (mm × mm)	FOV (mm)	Acq. time per image (s)	Number of slices orientation	Echo time
110/10	20	144 × 144	5	1.36 × 1.36	196 × 196	5.3	3/coronal	10 ms

further away. Unconfined mechanical loading was performed with an Electropuls Dynamic Test System E3000 (Instron, Norwood, MA, USA). The tests were performed in a custom-made chamber allowing to keep the sample at 33 °C. Sinusoidal loading at a frequency of 1 Hz, corresponding to walking frequency, was applied on each sample with 15% strain amplitude. This strain corresponds to the mean value of cartilage deformation during stance phase of gait (Liu et al., 2010). A 5% pre-strain was applied to insure full contact with the sample. The samples were first subject to 100 cycles as preconditioning. The dissipation power was calculated from the load-displacement graphs as the integral of the area enclosed by the 100th hysteresis curve multiplied by the frequency of stimulation. The dynamic stiffness was defined as the slope between the maximum load-displacement and minimum load-displacement. A t-test was used to examine the difference in dissipation and dynamic stiffness between the samples punched close to the site of degeneration and the others. The normality of the distribution was verified with normality probability plots (data not shown).

#### 2.4. Heat capacity of cartilage obtained with differential scanning calorimetry (DSC)

Heat capacity of human cartilage samples ( $n=3$ ) was determined using DSC following the method of McHugh et al. (2010). Briefly, the DSC heat flow signal from the sample was recorded between 10 °C and 60 °C with a heat rate of 10 °C/min using a differential scanning calorimeter MDS-Q100 (TA Instruments, New Castle, DE, USA). The DSC signal was compared to the DSC signal of

sapphire calibration standard, which specific heat is known. Both curves were corrected by a baseline correction experiment. The heat capacity of cartilage was then calculated as follows:

$$C_{p,\text{cartilage}}(T) = \frac{m_{\text{sapphire}}}{m_{\text{cartilage}}} \frac{\varphi_{\text{cartilage}}(T) - \varphi_0(T)}{\varphi_{\text{sapphire}}(T) - \varphi_0(T)} C_{p,\text{sapphire}}(T) \quad (7)$$

$C_p$  is the specific heat capacity;  $m$  is the mass; and  $\varphi$  is the DSC output signal as heat flow rate.

#### 2.5. Time constant of cartilage heat transfer obtained by magnetic resonance thermometry

Proton resonance frequency shift (PRFS)-based MR thermometry (Delabrousse et al., 2010) was used on a 3-T clinical scanner (Siemens Magnetom Trio 3T TIM System, Erlangen, Germany) in order to determine the heat transfer time constant in cartilage. We performed MRI acquisitions on the right knee of four male subjects (age =  $30.3 \pm 3.8$  yr) using a CP Transmit/receive head coil with integrated preamplifier and 16 rungs (Siemens AG, Erlangen, Germany). Table 1 summarizes the lipid signal suppressed MR sequence. A MRI-acquisition of 20 min was initially performed to determine the stability of baseline PRFS temperature measurement in the resting knee cartilage of each subject. Afterward, each subject was asked to perform a physical activity, 20 floors up the stairs (800 steps in total) in order to initiate heating in knee cartilage, and a few minutes after the effort end-point another 20 min MRI-acquisition was started. For each dynamic MR acquisition, the reference phase map was calculated slice-per-slice as the average of first 5 dynamic

measurements to reduce the bias from the noise. In order to stabilize the knee and avoid artifacts due to movements, we used a fixation system, which was purely passive and made of plastic, resin and carbon (Fig. 2). Three thermal imaging slices were set parallel, approximately in the coronal plane at the level of the intercondylar eminence (Fig. 3). Differential temperature curves (but not absolute temperatures) can be obtained for each voxel of the tissue. A temperature evolution curve was calculated as the mean of the temperature curves of the five voxels tangential to the medial condyle, in order to keep the same selection criteria of representative voxels. The time constant of cartilage heat transfer for each subject was determined by linear regression of the temperature evolution curve, fitted on equation  $T(t) = A + B \exp(-t/C)$ . The inverse of the time constant of cartilage heat transfer corresponds to the constant  $a$  of Eq. (6).

### 3. Results

Human cartilage samples were subjected to cycling loading at 1 Hz. Stress–strain graphs showed hysteresis curves typical of



Fig. 2 – The stabilizing system of the knee for MRI acquisitions.

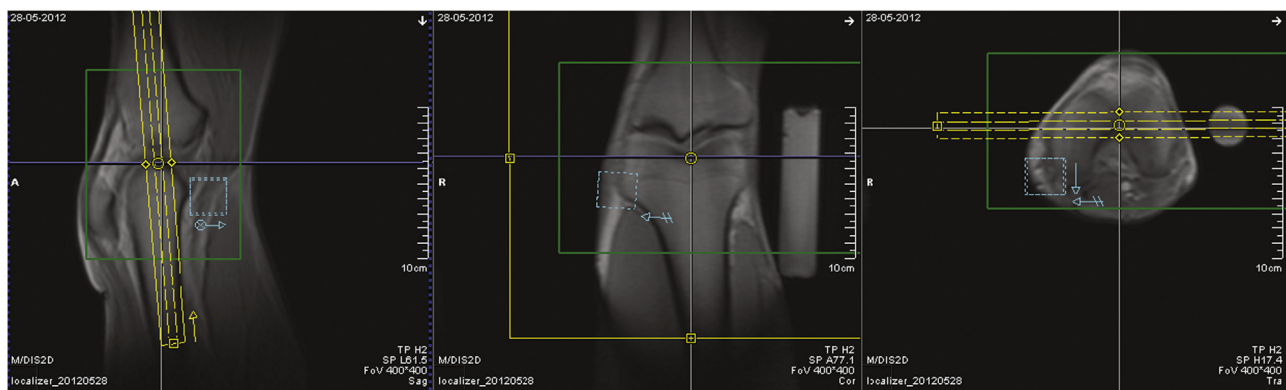


Fig. 3 – The thermal imaging slice, which was set in the coronal plane at the level of the intercondylar eminence. In yellow, the position of the acquisition plan and in green and blue the shim. Next to the knee is positioned a cylinder containing agarose gel, used as a constant reference to compare the differential temperature of cartilage. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

viscoelastic tissues (Fig. 4a), from which the corresponding energy dissipation were calculated as the integral of the area enclosed by the curve (Fig. 4b). The heat capacity of cartilage samples determined by DSC is reported in Table 2. It can be observed that heat capacity at 37 °C is higher than at 33 °C, but not with statistical significance. The differential temperatures of MRI acquisitions are shown in Fig. 5. For each of the four subjects a baseline curve was determined and it allowed us to verify the stability of baseline PRFS temperature measurements prior to physical effort. The temperature curves post-effort showed an exponential decrease of temperature. A curve fitting was performed for each curve to determine the time constant of cartilage heat transfer (Table 3).

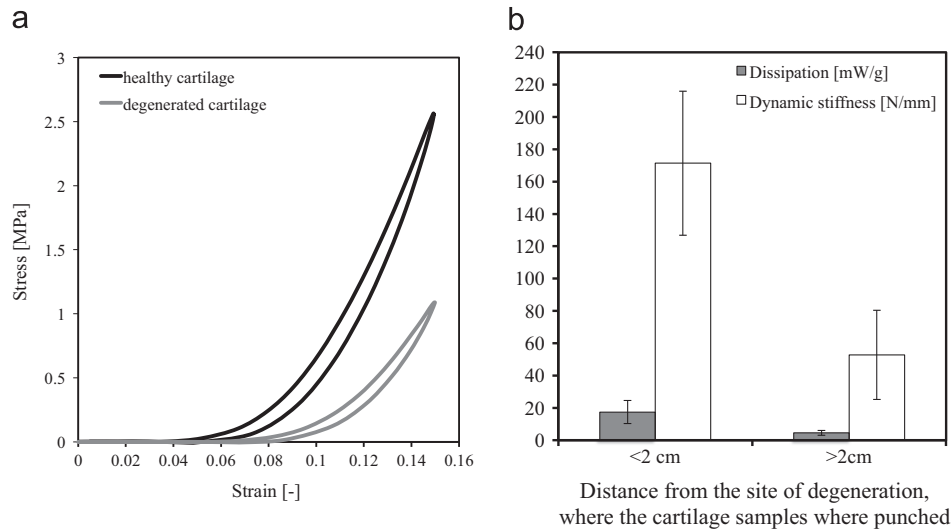
Temperature increase in articular cartilage during walking (Fig. 6) was calculated using Eq. (6) and incorporating the mean values of dissipation at 1 Hz for healthy and degenerated cartilage, as well as the mean values of time constant and heat capacity. For healthy cartilage samples, the model shows that dissipation may be sufficient to raise the temperature in articular cartilage from 33 °C to 36.7 °C after a 1 h walking. However, for degenerated cartilage the temperature augmentation did not exceed 1 °C. Indeed, a significant ( $p < 0.01$ ) decrease in the energy dissipation as well as in dynamic stiffness can be observed in degenerated samples that were punched less than 2 cm from the site of degeneration, as illustrated in Fig. 4b. Thus this decrease in dissipation implied also a reduced temperature increase during mechanical loading (Fig. 6).

### 4. Discussion

The evaluation of dissipation as an internal heat source to increase temperature in cartilage has not been reported in literature. Our results demonstrated that this phenomenon is important and can induce a consequent temperature increase in healthy cartilage.

The temperature measurement of the knee joint has a long history in medical thermometry (Ammer, 2012; Ho et al., 1994; Sanchez-Inchausti et al., 2005). However most of the measurements are based-skin (Becher et al., 2008; Oosterveld





**Fig. 4 – (a) Stress–strain curves of healthy and degenerated cartilage samples stimulated at 1 Hz and showing a typical hysteresis, characteristic of viscoelastic tissues. (b) Energy dissipation and dynamic stiffness of cartilage samples.**

**Table 2 – Heat capacity of cartilage samples ( $n=3$ ).**

Sample	Cp at 33 °C [J/(g K)]	Cp at 37 °C [J/(g K)]
Human cartilage	$3.99 \pm 0.18$	$4.11 \pm 0.16$

and Rasker, 1994) or are intra-articular (Martin et al., 2001; Warren et al., 2004), which cannot discriminate between heat generated by dissipation and heat generated by muscles and transported via the vascular system. Nevertheless, some studies have reported the increase of temperature subsequent to mechanical loading. Indeed, it has been shown that flexion-extension during 50 min on cadaveric human hip joint, having probes in acetabulum subchondral bone, increased the temperature up to 2.5 °C (Tepic, 1982). However, in this study no distinction was possible to determine if the temperature increase was due to intrinsic cartilage dissipation or friction between the joint surfaces. The author mentioned that the later was the cause of the observed temperature increase. Another study has reported the temperature measured in six healthy males, having a probe for intra-articular measurement inserted into the notch of the right knee. Median intra-articular temperatures increased by 4 °C and 5.8 °C after 30 and 45 min of jogging (Becher et al., 2008).

The advantage of our method is that it is non-invasive avoiding the implantation of probes with concomitant trauma and local anesthesia to knee, which have been shown to decrease performance in subjects and increase risk for knee injury (Becher et al., 2008). Moreover, the advantage of using a model to determine temperature increase is that it allows to integrate different heat sources, such as heat generated by muscles and transported via the vascular system, chondrocytes thermogenesis, or intrinsic dissipation. Each source could then be individually added in the model and its contribution can be evaluated independently. In our study we considered intrinsic dissipation as the only heat source.

A limitation of our method in characterizing heat transport is that it does not take into account heat convection via

interstitial fluid exudation during deformation, since the MRI measurement is acquired while the knee is stabilized. However, only little fluid exudation occurs in the middle and deep layers of articular cartilage (Hwang et al., 2008; Maroudas and Bullough, 1968; Stockwell and Barnett, 1964). Indeed, the ability of cartilage to support load through interstitial fluid pressurization is dependent on its low hydraulic permeability, which is nothing else that the ease of fluid flow through a material. For articular cartilage it is governed by the extra-cellular matrix and increases in the middle and deep zone with osteoarthritis (Hwang et al., 2008; Setton et al., 1994). Therefore, low heat transfer is expected via fluid-movement for normal healthy cartilage, while it may increase with tissue degeneration, sustaining our hypothesis that temperature increases in healthy cartilage but not in degenerated one. Another limitation of our study is the assumption of homogeneous temperature over the whole tissue, while in reality temperature gradients might be present in the tissue. However, the present model gives a first approximation of temperature evolution, since it sets the range of temperature increase. The model could be further refined by considering convection phenomena, spatial gradient of temperature or the contribution of other heat sources.

The choice of confined or unconfined configuration for evaluating the mechanical properties of cartilage is always debatable, especially in comparison to its physiological operating mode. In the present work an unconfined configuration was chosen. The cartilage sample was placed between two smooth frictionless impermeable plates, allowing its lateral expansion, which may occur physiologically. Indeed, a more physiological condition for testing the cartilage would be to consider a semi-confined situation, as done for other tissues such as the nucleus pulposus (Vogel and Pioletti, 2012).

In this study, we have shown that in degenerated cartilage the dissipation is decreased probably due to altered micro-structure and composition of the tissue, implying lower temperature increase when subject to mechanical stimulation. This result was supported with data obtained from

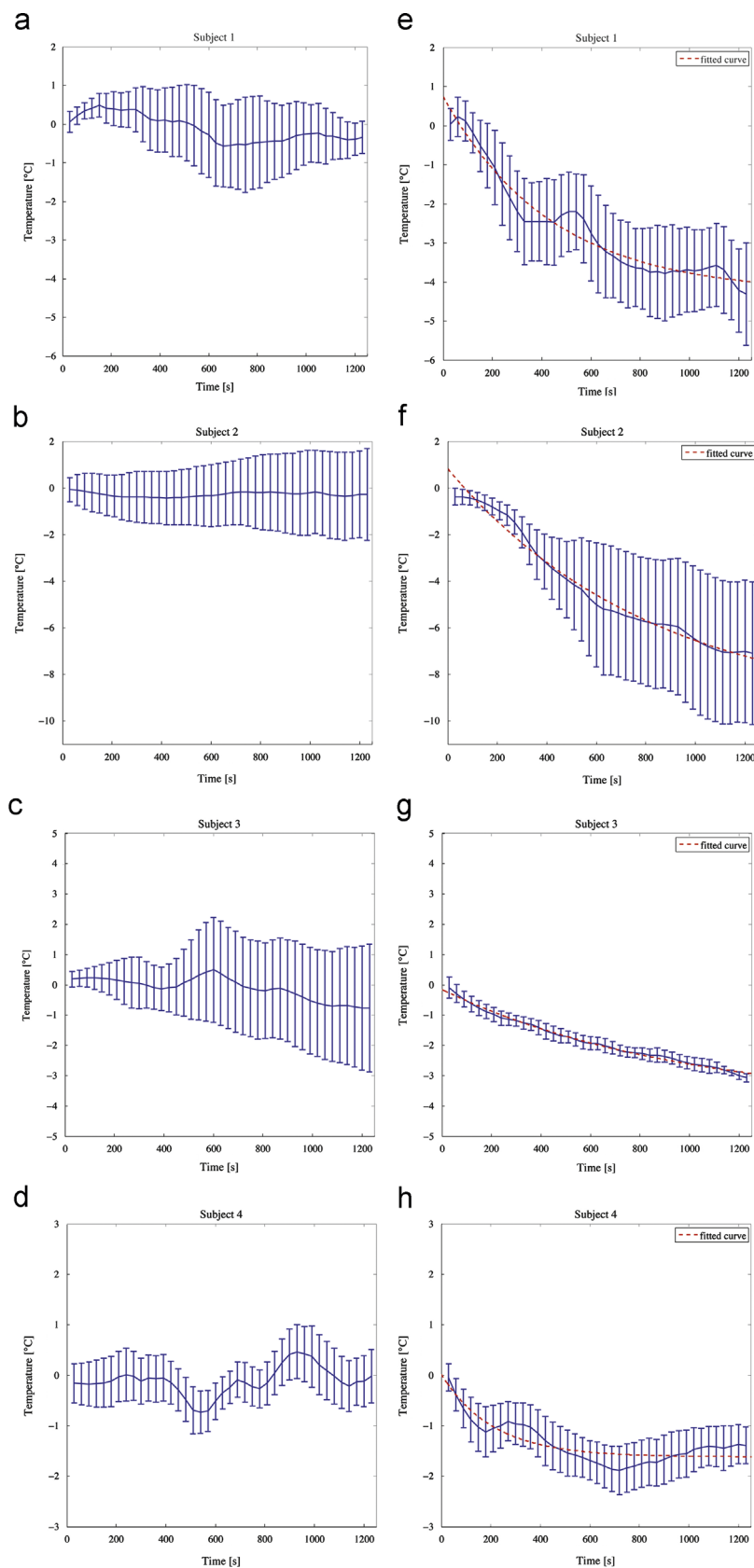
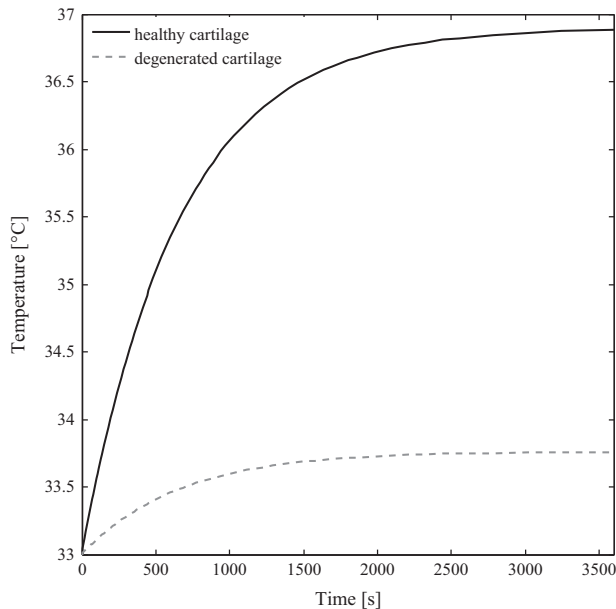


Fig. 5 – (a–d) Baseline of differential temperature curves for the four human subjects. (e–h) Temperature evolution curves and the corresponding fitted curves (red) for the determination of the time constant of cartilage heat transfer. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

**Table 3 – Time constant of the temperature evolution curve for each subject.**

Human subjects	Time constant [s]	R <sup>2</sup>
Subject 1	832	0.98
Subject 2	972	0.99
Subject 3	515	0.79
Subject 4	438	0.96
Average time constant	689 ± 254	–

**Fig. 6 – Curves of temperature increase due to dissipation in healthy and degenerated cartilage at the walking frequency of 1 Hz.**

healthy calf cartilage samples, and which were treated with collagenase solution, mimicking thus degenerative arthritis. The results showed that matrix depletion in cartilage sample implied dissipation and temperature diminution (Supplemental 1). The decrease of dissipation was associated with a loss of GAGs.

## 5. Conclusions

The goal of this study was to evaluate the temperature increase in articular cartilage due to its intrinsic viscoelasticity. We quantified the mechanical energy dissipated by human cartilage samples, its heat capacity, as well as the cartilage time constant of heat transfer using MRI-thermometry. Based on these experimentally determined parameters, we developed a mathematical model allowing the calculation of the cartilage temperature increase due to its intrinsic viscoelastic properties. We showed that dissipation may be sufficient to raise the temperature in knee cartilage from 33 °C to 36.7 °C after 1 h of walking. We showed in parallel that degenerated cartilage has a lower dissipation than healthy cartilage, which does not allow to generate a

significant temperature increase in the degenerated tissue. These results suggest a link between dissipative properties of the cartilage and its homeostasis.

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## Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at <http://dx.doi.org/10.1016/j.jmbbm.2013.10.025>.

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